

# A Computational Analysis of Interaction Energies in Methane and Neopentane Dimer Systems

THOMAS G. METZGER and DAVID M. FERGUSON\*

*Department of Medicinal Chemistry and Minnesota Supercomputer Institute, University of Minnesota, Minneapolis, Minnesota 55455*

WILLIAM A. GLAUSER

*Schroedinger, Inc., 17 Sheffield Drive, Maple Grove, Pennsylvania 19390*

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## ABSTRACT

The gas-phase interaction energies of methane and neopentane dimers are calculated at various intermolecular distances and geometries using several molecular mechanics and semiempirical parameter sets. For comparisons, a set of reference calculations are also performed using the 6-311G (2*d*, 2*p*) basis set with the inclusion of second-order Möller–Plesset energies (MP2) and basis set superposition corrections. These calculations are further used to examine the mechanism by which the AM1 and PM3 methods account for dispersion interactions in molecular systems. While no specific parameter(s) are included in semiempirical energy functions to capture such effects, the results indicate that both methods produce favorable interaction energies at near contact distances for the dimer systems. AM1 energies, however, show much closer agreement with the reference calculations, indicating potential deficiencies in the PM3 parameter set. Although the source of the dispersion energy could be traced to the attractive Gaussians of the core repulsion function in the AM1 Hamiltonian, a similar link could not be established for PM3. In contrast, PM3 dispersion energies apparently stem from a collection of contributions implicitly included during parameter optimization, providing no clear mechanism for correction or adjustment. Based on the analysis presented, an approach is also suggested for improving the AM1 parameter set. © 1997 by John Wiley & Sons, Inc.

\*Author to whom all correspondence should be addressed.

## Introduction

**N**onbonded interactions are the principle driving forces in most molecular recognition processes. While polar interactions (e.g., hydrogen bonds, salt links, etc.) are usually of primary interest, dispersion interactions also play a critical role, although less obvious, in determining many of the physical properties that affect molecular structure, conformation, and function. Despite their ubiquitous nature, these fundamental forces are often overlooked in molecular structure calculations. In fact, most *ab initio* molecular orbital calculations are restricted to the self-consistent field (SCF) level and therefore completely ignore correlation effects. Nevertheless, dispersion energies can be calculated with moderately large basis sets and the inclusion of correlation as estimated by single reference Möller–Plesset (MP) energies.<sup>1,2</sup> Of course, this inclusion comes at a tremendous price in computational intensity and, in many cases, is simply precluded due to system size. Molecular mechanics (MM) force field calculations, on the other hand, rely on an entirely different set of approximations to capture dispersion.<sup>3</sup> While  $1/r^6$ -based functions have become well accepted for modeling dispersion energies in MM force fields, the empirical parameters developed actually contain several components stemming from other second-order attractive effects.<sup>4,5</sup> System size limitations are typically not a problem, but the assumed transferability of parameters between systems is debatable.

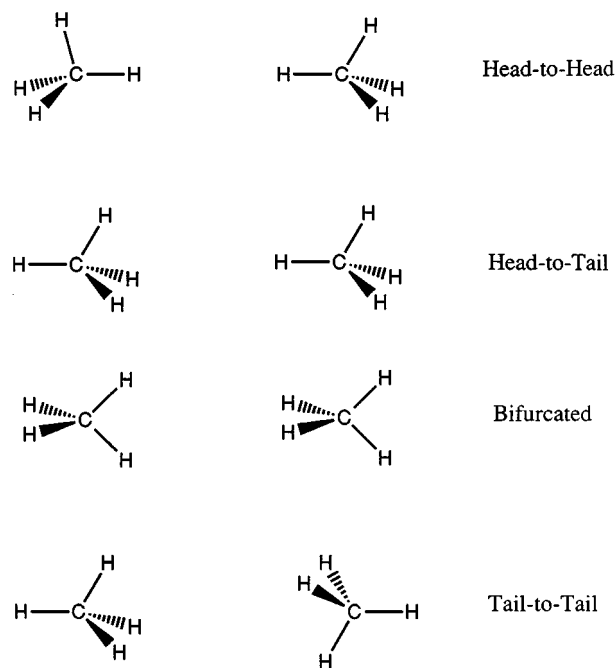
While semiempirical methods are often thought of as “bridging MM and *ab initio* calculations, it is important to point out that the basic formalism provides no clear description or inclusion of dispersion effects. Semiempirical methods based on the NDDO approximation simply make no allowance for correlation effects.<sup>6</sup> With the development of the MNDO method, however, it was believed that correlation effects could be implicitly included because one center repulsion integrals were based on experimental data.<sup>7</sup> Unfortunately, MNDO results demonstrated that the net effect was an overestimation of repulsions between atoms at approximately van der Waals distance apart. To remedy this, the core–core repulsion function (CRF), a classical expression accounting for nuclear–nuclear repulsion as well as exchange repulsion, was modified with additional attractive spherical Gaussian terms that could be considered

dispersion operators.<sup>8</sup> This was introduced in the AM1 Hamiltonian.<sup>9</sup> A third method, PM3, involved a simultaneous optimization of semiempirical parameters within the formalism of the NDDO approximation set by AM1 (i.e., Gaussian terms were included).<sup>8</sup>

To investigate these differing means of accounting for dispersion, we calculated the interaction energy of two simple apolar dimer systems, methane-methane and neopentane-neopentane. Both monomers possess zero dipole moments minimizing dipole–dipole and other second-order effects, thereby emphasizing the contribution of dispersion to the interaction energy. In addition, the methane dimer was previously studied with *ab initio* methods using moderately large basis sets and second-order MP (MP2) energies with success (as compared to available experimental data).<sup>10,11</sup> These MP2 Hartree–Fock calculations are reproduced here as well and further serve as a standard of comparison for all other methods of calculation. *Ab initio* calculations were also performed on the neopentane dimer at the MP2 level with the 6–311G (2*d*, 2*p*) basis set to estimate its interaction energy and optimal contact distance. Equivalent configurations for both dimer systems were then calculated using three semiempirical parameter sets (MNDO, AM1, and PM3) and three molecular mechanical force fields (MM2,<sup>12</sup> MM3,<sup>13</sup> and AMBER<sup>14</sup>) to determine the orientation dependence as well as the interaction energies of the systems. With regard to the semiempirical methods, an analysis of the effects of the CRF Gaussians of AM1 and PM3 was also performed to assess their contribution to dimer interaction energies. Based on these results, the means by which the different NDDO methods account for dispersion were compared.

## Methods

Methane dimers were model built in four different interaction geometries as shown in Figure 1. Monomer geometries were optimized with the 6–31G\* basis set using the Gaussian 92 program package.<sup>15</sup> Single point calculations were subsequently performed along the C–C internal coordinate separating these molecules at the 6–311G (2*d*, 2*p*) level with the inclusion of MP2 energies. The “counterpoise correction” method of Boys and Bernardi was also applied to estimate the magnitude of the basis set superposition error (BSSE)



**FIGURE 1.** The four orientations of the methane dimer used in this study.

inherent in each supermolecule calculation.<sup>16</sup> Although higher level basis sets are available for calculations of this type, the level applied here yields excellent results when compared with experimental data. In addition, this basis set is consistent with those used in parameterizing molecular mechanics force fields.

The MM calculations were performed in a similar fashion. Energy minimization was performed on each of the four geometries at a fixed C–C separation of 10 Å using the MM2 force field.<sup>12</sup> It was verified that the total energy of the dimer was twice that of the monomer energy. Next, initial energies were calculated for the dimer system at various fixed carbon–carbon distances. In other words, all coordinates from the 10-Å minimization were held fixed while the intercarbon distance was varied. At first energies were calculated every 1.0 Å until the near minimum, where energies were then calculated every 0.1 Å. The same analysis was performed with MM3.<sup>13</sup> Likewise, models for methane were built with the PREP, LINK, and EDIT modules of AMBER.<sup>14</sup> Energy minimizations were performed on the monomers using the MIN module of AMBER and the Cornell et al. force field.<sup>17</sup> Partial atomic charges for the monomers were taken from Pearlman and Kollman<sup>18</sup> and a constant dielectric of 1.0 was used throughout. Single point energy calculations were then per-

formed on the dimers at various fixed carbon–carbon distances with the ANAL module.

Semiempirical calculations were performed with the MOPAC 6.0 suite of programs.<sup>6</sup> Models for methane and its dimer were built with Z matrices. The Z matrix for the dimers contained a pseudobond between the central carbons whose value is fixed during minimization. Again, energy minimizations were performed at 10 Å for each input geometry, and then single point calculations were done at various intercarbon distances. Optimizations were done with the PRECISE program with the BFGS optimization algorithm. This scheme was performed with the MNDO, AM1, and PM3 parameter sets.

For the neopentane dimer, a similar scheme was used with respect to the various interaction geometries. Initial configurations were model built by substituting methyl groups for the hydrogen atoms of the four dimer geometries given in Figure 1. A fifth geometry was also included for neopentane in which the three nearest carbon atoms eclipse yielding a “tail to tail” eclipsed geometry. Monomer and dimer calculations for these five conformers were then performed using the same protocols as described above. The basis set calculations, however, were limited by the increased computational demands of this system. Each single point calculation (including BSSE correction) required approximately 10 Cray C90 hours to complete. The intense memory requirements of the calculations also proved problematic and often resulted in wall-clock times spanning several days. For this reason, *ab initio* interaction energies were only calculated for the tail to tail staggered geometry for this dimer system.

## Results

The results for the methane and neopentane dimers are summarized in Table I. In each case,  $r_{\text{opt}}$  refers to the intercarbon distance with the strongest interaction energy. Results for methane are for the dimer in the tail to tail configuration. The corresponding plots for methane and neopentane as calculated by the various methods are shown in Figures 2 and 3, respectively. MP2 calculations with the 6–311G (2d,2p) basis set yield interaction energies in close agreement with experimental results.<sup>10</sup> In general, the MM methods give energies and contact distances in good agreement with *ab initio* results. MM3 gives an optimal inter-

action energy in closer agreement with *ab initio* results than does MM2. The difference between MM2 and MM3 was found to lie primarily with the different parameters rather than with the modified function. This was verified by calculating interaction energies with the MM2 nonbonded function and MM3 parameters and vice versa. The Cornell et al. force field<sup>17</sup> used with AMBER yields the best agreement, which is surprising given the historical differences of the force fields applied. With respect to the orientation dependence of the interaction energy of the methane dimer, once again the MM methods gave excellent agreement with the *ab initio* results. Previous studies on the methane dimer showed that the tail to tail orientation gives the strongest interaction energy whereas the head to head geometry gives the most shallow well. The latter are also more repulsive at greater intercarbon distances than any of the other geometries.<sup>10,19</sup> This result was reproduced by each of the three MM methods examined here.

For neopentane, all of the MM methods displayed a preference for the tail to tail geometry (by analogy to the methane dimer). This interaction geometry was also used as the initial configuration for the *ab initio* calculations. The *ab initio* results for the neopentane dimer at several intermonomer distances are listed in Table II. The 6-311G (2*d*, 2*p*) basis set yielded an MP2 energy of  $-1.81$  kcal/mol at a central C-C distance of 5.2 and 5.3 Å, suggest-

ing that the minimum lies between these two distances. When the BSSE correction was applied, the interaction energies were  $-1.309$ ,  $-1.361$ , and  $-1.360$  kcal/mol at intermonomer separations of 5.2, 5.3, and 5.4 Å, respectively. This indicates that the separation distance yielding the lowest energy increases when the BSSE correction is applied. Such an effect was observed previously for the methane dimer<sup>11</sup> and is consistent with our methane results. It is likely that the BSSE corrected minimum for neopentane lies between 5.3 and 5.4 Å. Because we know of no similar studies with neopentane, these results serve as a "best estimate" and standard of comparison for the MM as well as semiempirical methods. Due to the computational demands of this system at the MP2 level, a complete search over various dimer configurations was not done. As in the methane case, the MM energies and contact distances showed good agreement with the *ab initio* result. A trend was apparent, however, indicating the MM force fields may overestimate the attraction. This may reflect methodological errors associated with pairwise potential energy functions or may simply reflect errors associated with the BSSE correction and/or the lack of optimization performed at the *ab initio* level. Further high level computations are therefore necessary to fully explore the disparities.

Although the MM calculations show similar energies and geometries, it is important to point out

**TABLE I.**   
Dimer Interaction Energies and Optimal Contact Distances.

	Method	$r_{\text{opt}}$ (Å)	Energy (kcal / mol)
Methane	MM2	3.5	0.91
	MM3	3.7	0.56
	AMBER	3.7	0.46
	AM1	—	—
	MNDO	—	—
	PM3	3.5	0.30
	MP2 / 6-311G (2 <i>d</i> , 2 <i>p</i> )	3.7	0.42
	MP2 / 6-311G (2 <i>d</i> , 2 <i>p</i> ) <sup>a</sup>	3.8	0.30
Neopentane	MM2	5.2	2.48
	MM3	5.3	1.75
	AMBER	5.2	2.02
	AM1	5.1	1.00
	MNDO	—	—
	PM3 <sup>b</sup>	4.9	6.80
	MP2 / 6-311G (2 <i>d</i> , 2 <i>p</i> )	5.2	1.81
	MP2 / 6-311G (2 <i>d</i> , 2 <i>p</i> ) <sup>b</sup>	5.3	1.36

Values are for the tail to tail orientation only.

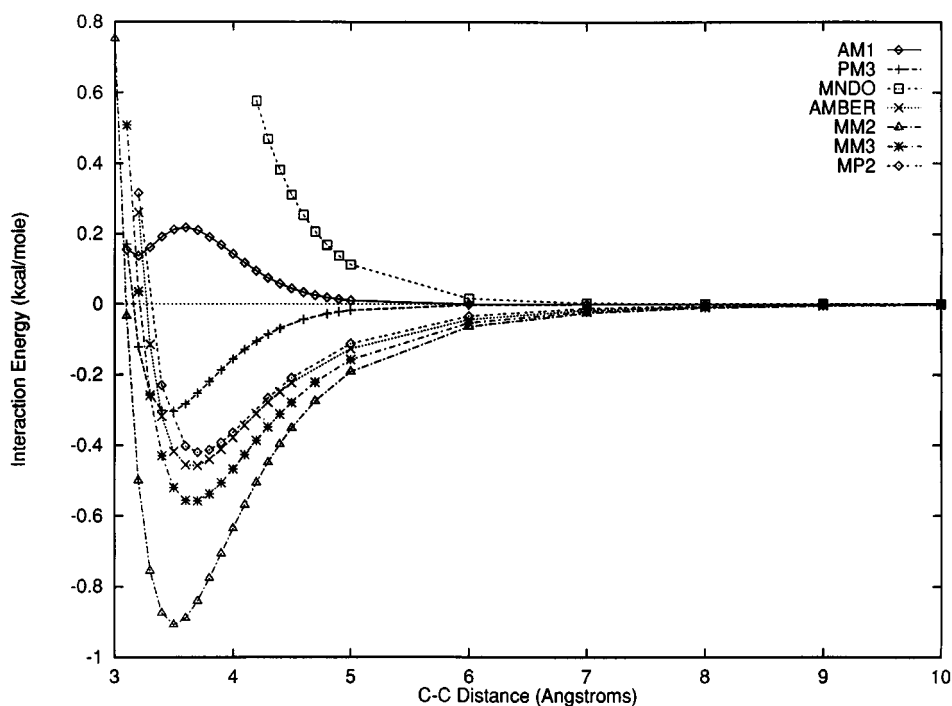
<sup>a</sup>With counterpoise correction.

<sup>b</sup>Approaching carbons are eclipsed in the tail to tail orientation.

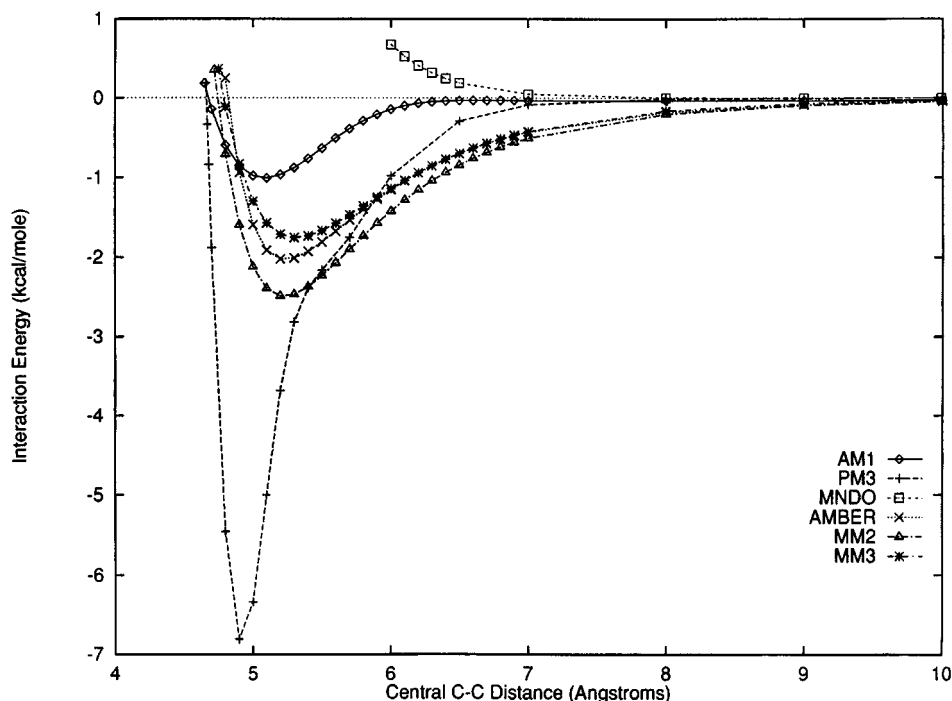
that the AMBER and MM2/3 force fields differ substantially in parameterization. MM2 and, by relation, MM3 were highly optimized for gas phase interactions, especially hydrocarbon-based molecules. AMBER, on the other hand, was developed mainly for condensed-phase simulations of polar molecules (mainly, biomolecules). To model polar interactions (including charged molecules), AMBER includes a Coulombic term that is parameterized with nontransferable partial atomic charges.<sup>17</sup> These charges, however, are not empirically adjusted during parameter set refinement. To examine for potential anomalous effects stemming from atomic charge-charge contributions, the dimer energies generated with AMBER were further decomposed into the Lennard-Jones (or van der Waals) and electrostatic terms. In the case of the methane dimer, the electrostatic term is strictly repulsive with a value of 0.038 kcal/mol at the  $r_{\text{opt}}$  for AMBER (3.6 Å). For neopentane, there is a modest electrostatic attraction of 0.016 kcal/mol at 5.4 Å. As expected, the overall energy curve closely follows the Lennard-Jones component for both dimer systems.

The semiempirical results are also reported in Table I. Unlike the MM force field models, the semiempirical energies are much more variable

and parameter set dependent. For the methane dimer, MNDO and AM1 give no interaction energy whereas PM3 gives a value in agreement with the MP2 values. These values, however, are for the methane dimer in the tail to tail orientation only. To investigate the orientation dependence of the methane dimer in closer detail, AM1 and PM3 interaction energy plots for the methane dimer in all four geometries were calculated and are shown in Figure 4. In particular, AM1 and PM3 give the strongest interaction energies for head to tail and head to head orientations, respectively. PM3 essentially reverses the trend set by the *ab initio* results. In the PM3 case, the head to head geometry gives a much greater interaction energy than any other configuration (see Fig. 4). AM1 gives somewhat mixed results, but, again, we should note shows no stabilization energy for the tail to tail orientation. Results for the neopentane dimer show a trend somewhat similar to that for the methane dimer. The MNDO surface has no energy well but the PM3 well depth is unrealistically high. In this case, the AM1 energy is in near-quantitative agreement with the *ab initio* result. For neopentane, it was found that the tail to tail geometry (by analogy to methane) gave the lowest interaction energy for all methods. However, PM3 results



**FIGURE 2.** Interactions energies for the methane dimer by the various methods. Values are for the tail to tail orientation defined in Figure 1.



**FIGURE 3.** Interactions energies for the neopentane dimer by the various methods. Values are for the tail to tail orientation in which the approaching carbons are staggered, except for PM3 where they are eclipsed.

showed a marked preference for the tail to tail geometry in which the approaching carbon atoms are eclipsed.

In part, these results can be explained by an analysis of the core-core repulsion functions used to model nuclear/core electron repulsions in semiempirical calculations. This function was modified in AM1 and PM3 to include several attractive Gaussian terms that were absent from the original MNDO Hamiltonian. Although the results indicate that these energy terms do, to some degree, act as dispersion force operators (as was

suggested<sup>8</sup>), the disparities may point to potential deficiencies in parameterization. Anomalous behavior of this term was noted in previous PM3 calculations. The attractive Gaussians were shown to produce an H-H interaction minimum at 1.80 Å,<sup>20</sup> very close to the proximal hydrogen separation of 1.7 Å in the head to head dimer geometry reported here. As our results also show, the effect of these Gaussians is further magnified ( $3 \times$ ) in the results for the neopentane dimer. The unique interaction geometry (tail to tail *eclipsed*) noted for PM3 may be better described as three head to head

**TABLE II.**  
***Ab Initio* Neopentane Dimer Interaction Energies.**

Intermonomer Distance (Å)	MP2 / 6-311G (2d, 2p) (kcal / mol)	MP2 / 6-311G (2d, 2p) with BSSE Correction (kcal / mol)
5.1	1.743	—
5.2	1.808	1.308
5.3	1.807	1.361
5.4	1.759	1.360

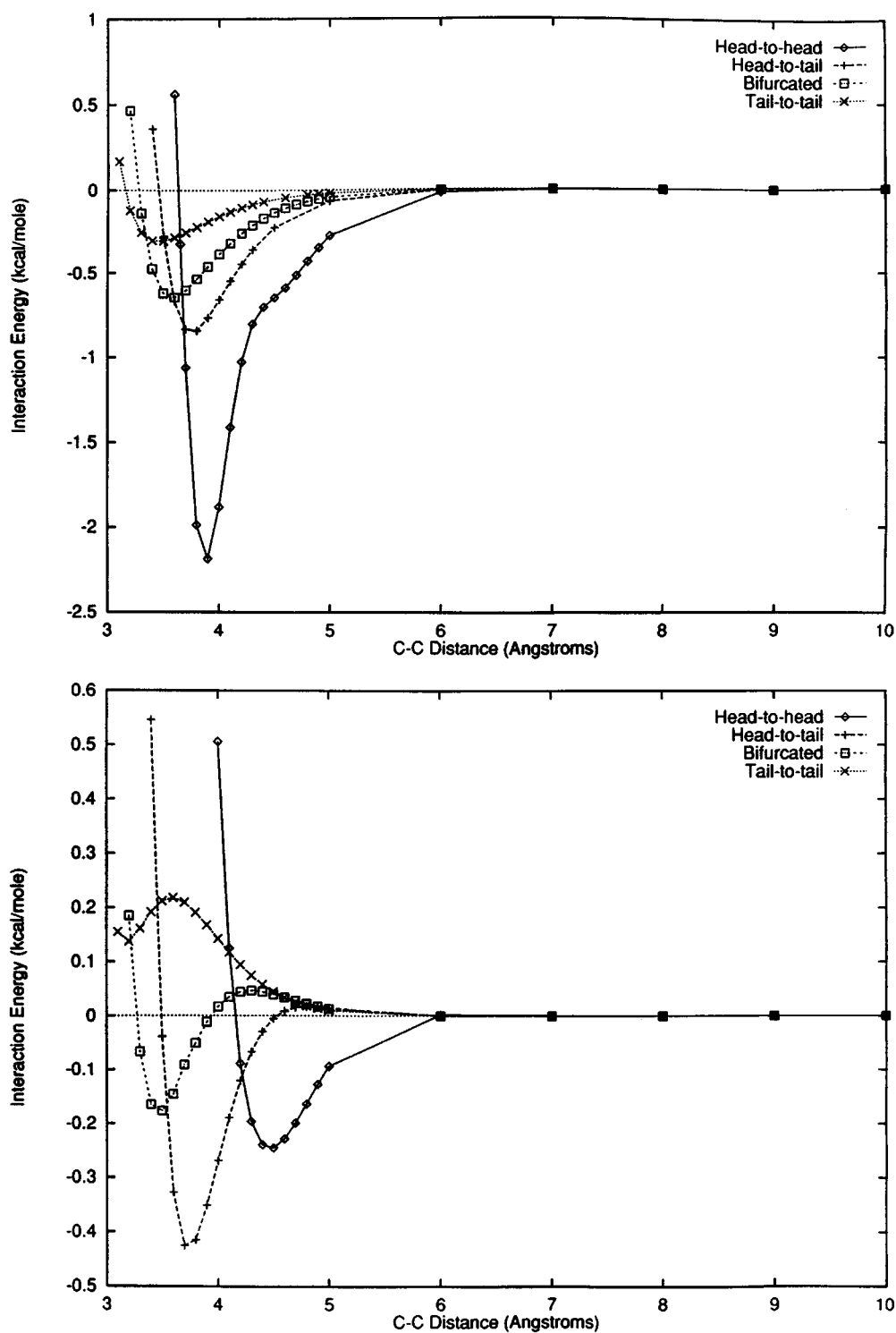


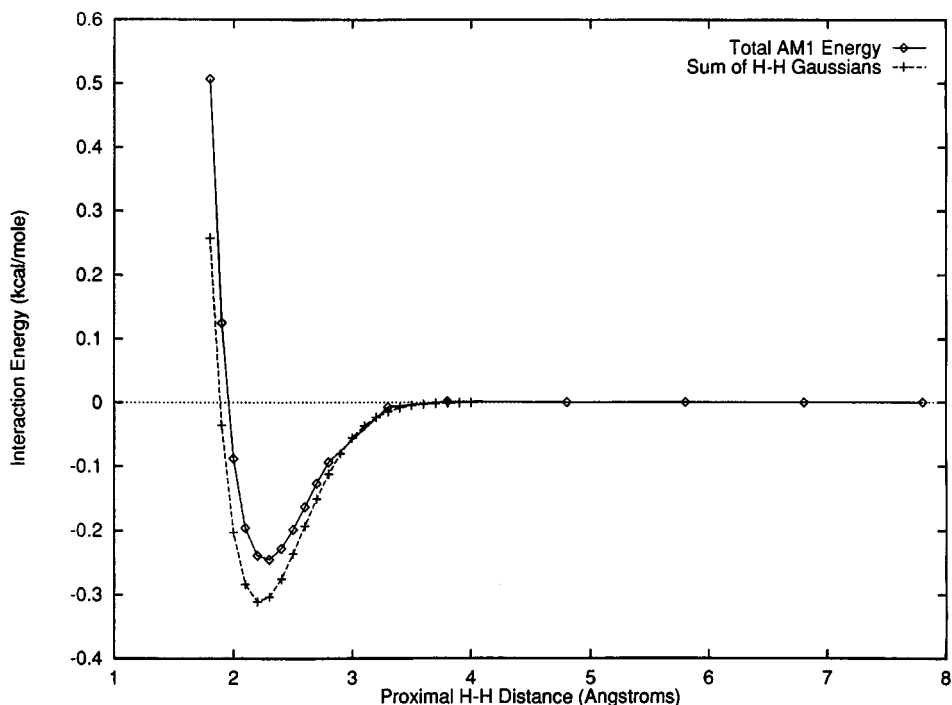
FIGURE 4. Orientation dependence of the interaction energy of the methane dimer. (a) AM1 and (b) PM3.

methane interactions. In the neopentane dimer, the approaching methane carbons are 3.86, 3.90, and 3.88 Å apart, with corresponding H–H interactions of 1.67, 1.71, and 1.69 Å. These distances closely mimic the methane dimer intercarbon separation of 3.9 Å and a head-on H–H distance of 1.73 Å noted for the head to head geometry.

Despite this effect, we hasten to add that a significant interaction energy was found by PM3 for the methane dimer, independent of the effects of the Gaussians in the CRF. For example, in the head to tail geometry the methane dimer had an interaction energy of 0.84 kcal at an intercarbon distance of 3.8 Å. In this dimer the closest H–H contact is 2.53 Å whereas the anomalous effects of the modified CRF for PM3 just described take place at an H–H distance of 1.6–2.0 Å. In short, it is clear that PM3 in some way accounts for dispersion interactions in the absence of the effects of the modified CRF. Aside from the particular cases involving close H–H contacts, the CRF Gaussians of PM3 do not contribute to the interaction energy at all. This is not the case, however, for AM1. Figure 5 shows a plot of the interaction energy of the methane dimer by AM1 in the head to head

geometry as a function of the proximal H–H distance along with a plot of the sum of the CRF Gaussian terms for an H–H pair at the given distance. It is noted that the magnitude of the attraction for the Gaussian terms is always at least as great as the interaction energy of the methane dimer. This strongly suggests that in the absence of the additional terms to the CRF, the AM1 interaction energy curve would look like that of MNDO. Likewise, the neopentane dimer at 5.1 Å has an interaction energy of 1.00 kcal where six H–H contacts between 2.33 and 2.38 Å provide approximately 0.3 kcal of CRF Gaussian energy stabilization per contact.

In comparing these results with those derived from MM, a decomposition of the latter into pairwise energies shows no single interaction greater than 0.055 kcal. Thus, the most stable MM configurations are those that maximize the relatively weak C–H and H–H pairwise attractions. By contrast, AM1 gives the strongest interaction energies for geometries that benefit from strong individual H–H interactions (via the CRF Gaussians) at longer C–C distances. This implies that as the C–C distance decreases (e.g., from 4.0 to 3.0 Å) the Gauss-



**FIGURE 5.** AM1 interaction energy of the methane dimer in the head to head orientation as a function of the proximal H–H distance compared to the energy of attraction of the Gaussians of the core repulsion function between hydrogen atoms.



ians attractive energy must compensate for the overall net repulsion, because the total energy increases as the C–C distance decreases (see MNDO plot). Meanwhile, the effect of the attractive Gaussians is negligible for all C–C interactions at nonbonded distances. (C–H interactions provided very slight stabilization.) This at least partly explains the preference for the head to head and head to tail geometries by AM1. In the case of the tail to tail geometry for AM1, it is evident that the stabilizing effects of the H–H CRF Gaussians contribute at C–C distances where the net of all other interactions is significantly repulsive. This can be seen as a slight dip in the methane curve for this geometry (Fig. 2) at an intercarbon distance of 3.2 Å while the total interaction energy remains above zero (i.e., twice the monomer energy).

It is difficult to compare the results for PM3 in a similar context. The parameter optimization in PM3 represents a more radical departure from the MNDO method (compared to AM1). In particular, PM3 involved an optimization of the one-center, two-electron repulsion and exchange integral parameters that were taken from atomic spectra in AM1 and MNDO. As stated previously, the parameters of semiempirical methods are so intimately interlinked that it is difficult to assess the effects of a single parameter. Therefore, it remains unclear which particular elements of the PM3 parameter set account for the interaction energies of the dimer systems not captured by MNDO.

## Conclusion

One of the main objectives of this study was to evaluate the means by which molecular mechanical and semiempirical methods capture dispersion interactions in nonpolar systems. The results of these methods were compared to those generated with the 6–311G (2*d*, 2*p*) basis set at the MP2 level for the interaction energy of the methane and neopentane dimers. While the MM methods regularly produced results consistent with those of the *ab initio* methods, the semiempirical methods produced a variety of results. The MNDO method yielded no interaction energy for either dimer system with any orientation geometry. This was not unexpected because the MNDO Hamiltonian includes no explicit or implicit means of capturing dispersion. AM1 produced results in reasonable quantitative agreement with those from the *ab initio* method but produced inconsistent results in

terms of the orientation dependence for the methane dimer. The PM3 Hamiltonian gave stronger interaction energies than any other method for both methane and neopentane dimers.

Clearly the three semiempirical methods based on the NDDO approximation included in this study differ in their method of estimation of dispersion. The results seen for AM1 are best explained with reference to the attractive Gaussian terms in the CRF not found in MNDO. Although AM1 and MNDO possess different parameters, it is apparent that the parameters were sufficiently similar such that the modified CRF represents the major difference in their treatment of dispersion as measured by the interaction energy of the hydrocarbon dimers. By contrast, PM3 gives interaction energies for the dimer systems that were not a result of the modified CRF. Unlike AM1 and MNDO, all parameters in PM3 are significantly different from their AM1 and MNDO counterparts because they were fully optimized. Because the methods based on the NDDO approximation have no coherent model for dispersion interactions and adjustment of any single parameter would have wide ranging and unpredictable effects, it is difficult to suggest modifications that would yield a more well-behaved dispersion model. One possibility would be an adjustment of the AM1 model that would allow a reduced C–C repulsion at van der Waals distances in conjunction with a reduction in the magnitude of the H–H CRF Gaussian attraction so that systems with greater numbers of relatively weak interactions would be stabilized. The reproduction of the anisotropic effects in the methane dimer could serve as a useful test in the development of future semiempirical methods.

Although the MM results were, to some extent, expected at the outset, the general applicability of AMBER to model interactions of this type is noteworthy. Whereas MM2/MM3 were primarily optimized for calculations of small to medium sized organic molecules in the gas phase, the Cornell et al. force field was developed for condensed phase simulations of large polar molecules.<sup>17</sup> The nonbonded van der Waals parameters for aliphatic carbons and hydrogens in the latter were derived from liquid simulations of small hydrocarbons. The results presented here indicate that these parameters are transferable to modeling aliphatic interactions in gas-phase environments as well, further affirming and extending the general applicability of this force field and parameterization to simulating molecular systems. Similar transferabilities were not shown for small polar molecules.

This is most likely due to the greater and more complex role other second-order effects (i.e., charge transfer, polarization, etc.) play in determining molecular interactions and energies in systems of that type.<sup>5</sup> For completeness, we also repeated the calculations using the Weiner et al. force field originally released with the AMBER program package.<sup>21</sup> Although not reported here, the results show a consistent underestimation of interaction energies ( $\approx 20\%$ ) and contact distances for the dimers. While our analysis is limited, it is reasonable to conclude that both second generation force fields applied here (MM3 and Cornell et al.) provide improved descriptions of dispersion energies as well as interaction geometries in simple hydrocarbon systems. Given the close packing of hydrophobic residues in protein cores and the pervasive nature of aliphatic groups in determining molecular structure and conformation, the differences may be significant in many other MM applications as well.

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